REMARKS

This amendment is submitted in an earnest effort to bring this application to issue without delay.

Applicants wish to reiterate their claim to the benefit of their German priority date of 2 October 2003 pursuant to the International Convention. Applicants have made of record a certified copy of German Patent Application 103 46 487.5 filed 2 October 2003 in their PCT/DE2004/002197 filed 1 October 2004 of which the instant application is the US National Phase. The Examiner has already acknowledged the Applicants' perfected right of priority.

Applicants have amended page 6, line 31 to page 7, line 1 of the specification in order to correct some minor informalities, including referring to specific claim numbers in the Summary of The Invention. In addition the Applicants have augmented the Summary of the Invention at the same point in the specification in order to more clearly define the invention and provide the antecedent basis in the specification for the claims now presented. Antecedent basis for the amendments to the specification may be found in claims 1 and 2 as originally presented. Applicants have inserted no prohibited new matter into the application by making these amendments to the specification.

Applicants have amended claim 2. Antecedent basis for the amendments to claim 2 may be found in claims 1 through 3 as

originally presented as well as in the specification on page 31, lines 14 to 23, especially line 20 where the catalytic domain appears in lower case nucleotides and the left and right substrate binding domains adjoining the 5'- and 3'-ends of the catalytic domain appear set off in upper case polynucleotides. Thus claims 2 through 8 remain in the application and are presented for examination.

The Examiner has rejected claims 2 through 8 as last presented under 35 USC 112, first paragraph, on the grounds that the specification does not adequately disclose the invention to the extent necessary to establish that the Applicants were in possession of the claimed genus according to the invention as claimed in the claims presently on file by the disclosure set forth in the International Application at the time of the filing of the International Application on 1 October 2004.

Applicants have sharply limited claim 2 and the claims dependent thereon so that the claims of this narrower scope are clearly supported by the specification with respect to the disclosure requirements of 35 USC 112. Note that in the DNAzymes now within the scope of claim 2, the definition of the right substrate binding domain adjoining the 3' end of the catalytic domain has been limited to polynucleotide sequence GTCTTGGAG and that the definition of the left substrate binding domain adjoining the 5' end of the catalytic domain has been limited to polynucleotide sequence GTGGATGGA. Now that both of the substrate

binding domains have been limited to specific polynucleotide sequences, the term "respectfully complementary" regarding hybridization of the two binding domains to the GATA-3 mRNA in order to functionally deactivate same is clearly supported by the disclosure in the specification even though the structure of the RNA in the GATA-3 mRNA is not specified. Since the DNA structure of each of the two binding domains is clearly specified and since the RNA in the GATA-3 mRNA must be complementary to the DNA in each of the binding domains, Applicants have clearly disclosed enough information about the RNA so that one skilled in the art would know enough about the RNA structure undergoing hybridization with the two binding domains of the DNAzymes according to the presently claimed invention so as to be put into possession of the presently claimed invention.

Applicants have not, however, amended claim 2 to limit that claim to DNAzymes that require the polynucleotide of SEQ ID NO: 154 as the catalytic domain. Applicants note the Examiner's point that the specification does not specifically define what Applicants mean by "a modified sequence with comparable biological effect", but nonetheless have retained in claim 2 the language "...nucleotide sequence GGCTAGCTACAACGA SEQ ID NO: 154 or a modified sequence with comparable biological effect, which cleaves the GATA-3 mRNA at every purine:pyrimidine binding site to which it is bonded...". Applicants point out that the 10-23 DNAzyme with the catalytic core GGCTAGCTACAACGA SEQ ID NO: 154 is disclosed in

Santoro et al, "A general purpose RNA-cleaving DNA enzyme"; Proc. Nat. Acad Sci. USA, Vol.4, pp 4262-4266, April 1997. The 10-23 DNAzyme has the same catalytic domain as the presently claimed DNAzymes. See Figure 2, at the top, right of page 4264 and see page 4565 in the paragraph bridging the left-hand column and the right-hand column. According to the reference, it is known in the art which nucleotide substitutions are permitted to this very same catalytic domain in order to retain the DNAzyme catalytic activity with respect to cleaving mRNA. Apparently the eighth nucleotide in the catalytic domain, which is a T, may be replaced by either a C or an A nucleotide and still good catalytic activity may be retained. In view of the Santoro et al article, Applicants contend that one "skilled in the art" having the present application and the Santoro et al publication as well is put into possession of the invention as presently claimed in claim 2.

In view of the above Applicants ask that the Examiner no longer maintain rejection of claim 2 or the claims dependent thereon under 35 USC 112, first paragraph, as based upon a specification that fails to meet the statutory "written description requirement."

Applicants appreciate the Examiner's indication that claim 3 is free of the prior art and that there is no basis to reject claim 3 as either anticipated under 35 USC 102 or as obvious under 35 USC 103. However, the Examiner did indicate in the office

action that claim 3 must also be free of the issues that she has raised under 35 USC 112, first paragraph, with respect to whether the specification provides enough information to put one "skilled in the art" in possession of the invention. For the reasons set forth in this amendment herein above, Applicants believe that claim 3 as well as claims 2 and 4 through 8 are supported by a specification that sufficiently describes the invention so as to put one "skilled in the art" in possession of the invention. Thus at the outset Applicants believe that claim 3 is in condition for allowance.

Furthermore Applicants believe that claims 2 and 4 through 8 as now presented are in condition for allowance as well. Applicants have already explained why claim 2 and all claims dependent thereon are in compliance with the disclosure requirements of 35 USC 112, first paragraph. Furthermore Applicants believe that claims 2 and 4 through 8 are patentably distinguishable over the prior art for the same reasons that claim 3 is patentably distinguishable over the prior art in view of the fact that Applicants have limited the scope of both of the binding domains flanking the catalytic domain of the DNAzymes presently claimed. There is no suggestion in the prior art of a DNAzyme having the two binding domains of the indicated polynucleotide structures that flank the catalytic domain. Thus Applicants believe that no claim now presented should be rejected as obvious under 35 USC 103 in view of the prior art.

Applicants now wish to make the following direct arguments with regard to the claims now presented to patentably distinguish over the cited prior art.

All claims as now presented require that the binding domains that flank the catalytic domain in the DNAzymes are limited to the polynucleotide GTGGATGGA at the 5'-end of the catalytic domain and to the polynucleotide GTCTTGGAG at the 3' end of the catalytic domain. These two polynucleotides that flank the known central catalytic domain GGCTAGCTACAACGA or its known modified sequences as disclosed in SANTORO et al, result in DNAzymes that are structurally distinguishable from those of the prior art. Thus all claims now presented are directed to novel DNAzymes that include both the polynucleotide sequence of the central catalytic domain, and also the two substrate specific polynucleotide sequences, which allow direct classification n of a target mRNA as well as the position of the DNAzyme binding with the target mRNA.

Thus no claim now presented should be rejected as anticipated under 35 USC 102 in view of the SUN et al reference.

In addition the presently claimed invention would not have been obvious to those skilled in the art in view of the combination of IMAGAWA et al and SUN et al. As the Examiner points out IMAGAWA et al teach inhibition of GATA-3 mRNA with antisense oligonucleotides. SUN et al teach the design of DNAzymes with a catalytic core identical to the catalytic core in the present SEQ ID NO: 154.

The catalytic core of the DNAzymes disclosed in SUN et al consists of the same 10-23 catalytic motif GGCTAGCTACAACGA, which is the same as the catalytic domain employed according to the presently claim ed invention.

The substrate specificity of these kinds of DNAzymes is not caused by the catalytic domain. In fact, gene specific sequence regions, left hand and right hand of the central catalytic region are crucial for specific binding to an RNA substrate. A scheme of the composition of such a DNAzyme and the way in which complementary sequence binding is illustrated in Figure 2 of the present invention.

A pool of 70 newly designed DNAzymes (designated hgd1 through hgd70) was tested for the ability of the individual DNAzymes to cleave GATA-3 mRNA. All of the DNAzymes consist of the same central 10-23 catalytic motif. The DNAzymes differ in the sequence specific regions to the left and to the right of the central catalytic domain. See Figure 3.

The ability of such a DNAzyme to cleave mRNA is not predictable. Some regions of the target mRNA might be blocked by secondary RNA structures and are thus inaccessible to DNAzymes. Therefore, several DNAzymes were generated, using different parts of the target mRNA to ensure access for the DNAzyme to the mRNA.

Each of the 70 designed DNAzymes had to then be tested individually for its cleavage activity on the target mRNA. The extensive work, comprising template generation, DNAzyme generation, and all cleavage testing experiments are disclosed in the present invention (cf. Example 1 and Example 2). It is therefore not possible to simply choose randomly a region of the preferred target sequence and to generate only one DNAzyme.

Figure 5 shows the results of the cleavage experiments. Using gel electrophoresis the cleavage activity of the DNAzymes for GATA-3 mRNA is illustrated. The comparison of all 70 DNAzymes shows that hgd11, hgd13, hgd17 and hgd 40 have a very high cleavage activity whereas other DNAzymes have a lower cleavage activity or no cleavage activity at all. These results are summed up in the corresponding table (Example 1, description of Gig. 5). Thus, all of the designed 70 DNAzymes were tested individually for their activity.

In view of the non-predictability of the cleavage activity of various DNAzymes, the presently claimed invention would not be obvious for one skilled in the art. None of the cited prior art references, taken alone or in combination, discloses or suggests the presently claimed invention.

Applicants believe that all claims now presented are in condition for allowance and earnestly solicit a response to that effect.

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Enclosure: Santoro et al reference on Catalytic Domains